EDITORIAL

Why does the heart rate response to exercise predict adverse cardiac events?

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The physiological mechanisms responsible for determining heart rate during exercise are complex, and further research into ''chronotropic incompetence'' is clearly required

Exercise testing is a simple and inexpensive diagnostic tool that is performed routinely in every cardiology department. It is primarily used to look for the presence of myocardial ischaemia, but provides further valuable information that is not widely appreciated. Examination of the heart rate during exercise is of powerful prognostic value. In 1975 Ellestad and Wan showed that the lack of an appropriate heart rate response to exercise, a feature they termed ''chronotropic incompetence'', was associated with a greater risk of adverse cardiac events in the next five years than was ST segment depression.[1] Many further studies have confirmed that chronotropic incompetence is an independent predictor of risk in patients with coronary artery disease; although inferior to myocardial perfusion scanning in the prediction of cardiac death, it does add incremental prognostic value to this test.[2] Chronotropic incompetence is also predictive of adverse cardiac events and total mortality in apparently healthy individuals even after adjustment for factors such as age, ST segment shift, physical activity, and traditional coronary disease risk factors.[3] Further confirmation of the prognostic value of the heart rate response to exercise has been demonstrated in a recent study of nearly 6000 healthy male Parisian civil servants who underwent exercise testing between 1967 and 1972.[4] A low heart rate response to exercise proved to be a powerful predictor of both sudden death and total mortality though not of death from ''non-sudden myocardial infarction''. This finding was particularly striking as the lack of heart rate response in these individuals was relative; subjects who achieved less than 80% of their predicted maximum predicted heart rate were excluded from the study.

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CHRONOTROPIC INCOMPETENCE

Why does chronotropic incompetence predict adverse cardiac events? In this issue of *Heart*, Huang and colleagues[5] show that in subjects undergoing investigation for angina, individuals with a low chronotropic index (a measure of heart rate response that corrects for exercise capacity) had impaired endothelial function, raised markers of systemic inflammation, and raised concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) compared to those with a normal heart rate response. These findings were not explained by demographic or conventional risk factors. This is clinically relevant as endothelial function and markers of inflammation are also markers of prognosis and are closely involved in the control of plaque stability and thrombogenicity. This is new and important information but the authors can only speculate about the underlying mechanisms. Their study provides many valuable pointers to further research. Is there a common pathway that results in abnormalities of prognostic markers as diverse as chronotropic incompetence, endothelial function, markers of systemic inflammation, and BNP? Alternatively, is one of these factors, perhaps systemic inflammation, the primary abnormality underlying chronotropic incompetence? These questions are particularly difficult because the physiological mechanisms responsible for determining heart rate during exercise are complex and poorly understood. In fact, the cause of chronotropic incompetence remains unknown, some 30 years after the first demonstration of its clinical importance.

It has been suggested that chronotropic incompetence is a manifestation of abnormal cardiovascular autonomic control and provides information that is analogous to that of low heart rate variability (HRV) or baroreflex sensitivity (BRS). A large body of experimental animal and human clinical research supports the concept that cardiac autonomic nervous control is a powerful determinant of susceptibility to sudden cardiac death. Reduced vagal and increased sympathetic activity appears to increase the risk of ventricular arrhythmia.[6] Reductions in HRV and BRS are indicative of impaired cardiac vagal control and are powerful independent markers of an adverse prognosis after myocardial infarction. While the autonomic nervous system is of prime importance in determining the heart rate response to exercise, no good evidence exists showing that chronotropic incompetence is caused by impaired cardiac autonomic control. The relation between markers of cardiac autonomic control such as HRV and BRS and heart rate during exercise has not been examined. Furthermore, a simple ''autonomic balance'' theory of chronotropic incompetence would predict that subjects at

Abbreviations: BRS, baroreflex sensitivity; HRV, heart rate variability; NT-proBNP, N-terminal pro-brain natriuretic peptide

increased cardiovascular risk would have higher, not lower, heart rates during exercise. Standard exercise physiology teaches that the onset of exercise is followed by abrupt vagal withdrawal and an increase in sympathetic input to the sinus node as a result of central command and afferent signals from receptors in contracting muscles. The baroreflex is inhibited, allowing a simultaneous increase in blood pressure and heart rate. Abnormalities in autonomic control of heart rate during exercise could originate at any point within the muscle heart reflex pathway. An impaired heart rate response to exercise could be explained by paradoxically high levels of vagal control and/or reduced sympathetic drive during exercise. Could individuals with severe coronary artery disease and systemic inflammation have a central or peripheral abnormality of autonomic control? The influence of inflammation on autonomic control is largely unknown, but it is quite possible that inflammatory cytokines might exert powerful effects.

COMPENSATORY PARASYMPATHETIC HYPERACTIVITY

A ''compensatory parasympathetic hyperactivity'' during exercise has been suggested as an explanation for chronotropic incompetence before.[7] There is evidence to show that vagal control is not withdrawn completely during exercise and that baroreflex control of heart rate is not abolished but is reset and operates at a point on the curve that allows reduced gain.[8] Could chronotropic incompetence therefore be due to failure of resetting so that inappropriate vagal activation occurs during exercise? Vagal stimulation during exercise due to afferents from left ventricular mechanoreceptors stimulated by the abnormal contraction of an ischaemic ventricle has been suggested. Cardiac vagal control, particularly during exercise, certainly requires further investigation in subjects with chronotropic incompetence, but there is no obvious connection between excess vagal control during exercise and systemic inflammation or impaired endothelial function. Indeed, vagal activity appears to result in an anti-inflammatory action.[9]

Alternatively, chronotropic incompetence could be a manifestation of sinus node β receptor down regulation as a result of chronic sympathetic activation. One reason for this which was not examined by Huang and colleagues[5] might be impaired left ventricular systolic or diastolic function in the group with chronotropic incompetence; this might also explain the NT-proBNP results. It is now clear that the metabolic syndrome is also associated with sympathetic activation, particularly if hypertension is present.[10] Patients with metabolic syndrome exhibit most of the features described by Huang and colleagues[5] in their patients with chronotropic incompetence, namely impaired endothelial function and systemic inflammation with raised concentrations of inflammatory markers and cytokines. They are also of course at high risk of adverse cardiovascular events. The possibility that chronotropic incompetence is a surrogate marker for raised sympathetic activity caused by ventricular dysfunction or metabolic syndrome deserves investigation.

SINUS NODE DYSFUNCTION

Intrinsic sinus node dysfunction seems at first sight an unlikely cause of chronotropic incompetence. It is a common cause of dizzy turns and syncope in the elderly but does not appear to be associated with coronary artery disease or an adverse prognosis. The suggestion that heart rate control is impaired in individuals with severe coronary artery disease as a result of sinus node ischaemia is a hypothesis that has been tested and so far refuted.[7] It is possible, however, that chronotropic incompetence might be caused by reduced bioavailability of nitric oxide within the sinus node. Animal experiments and our own studies in human heart transplant recipients have shown that nitric oxide (NO) exerts a tonic chronotropic effect on the sinus node probably by causing reduced activation of the I_f current.[11] In patients with coronary artery disease and/or systemic inflammation, endothelial NO bioactivity is impaired as a result of reduced synthesis and inactivation by reactive oxygen species. Patients with the greatest reduction in sinus node NO bioavailability might also be expected to demonstrate impaired vascular endothelial dysfunction and perhaps systemic inflammation.

Further research into chronotropic incompetence is clearly required. The factors that control heart rate during exercise in health and disease require intensive investigation, as do the complex interrelationships between the autonomic nervous system and the immune system. While molecular and cellular techniques will provide valuable information, the primary need is for well conducted integrative physiological studies. This is not ''translational'' or ''bench to bedside'' research but clinical physiology of the sort that has become unfashionable. Many UK medical schools have now closed their physiology departments and concentrated their efforts on cellular and molecular laboratories, leaving few centres with the necessary expertise to investigate abnormalities such as chronotropic incompetence. Huang and colleagues[5] have provided an excellent example of why our research institutions should rekindle their enthusiasm for clinical physiology. In the meantime, lack of understanding should not prevent clinicians from using this observation to aid risk stratification in patients undergoing exercise testing.

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